Date: December 16, 1997

From: Gibbes Johnson, Ph.D.

To: BLA #96-1408 File

Through: David Finbloom, M.D.

Re: Review of Biologics License Application #96-1408
Sponsor: OMJ Pharmaceuticals
Scientific Name: Platelet-Derived Growth Factor-BB
USAN or Proper Name of Drug Substance: Becaplermin
Final Drug Product Name: Regranex
Indication: Diabetic Foot Ulcers

OMJ BLA #96-1408

Volume 3

Chapter 4: Chemistry, Manufacturing and Controls

I. Drug Substance

The drug substance, becaplermin, is manufactured by Chiron Corporation in Vacaville and Emeryville, CA (associated BLA#961422) and formulated by OMJ Pharmaceuticals in San German, Puerto Rico.

II. Drug Product

Composition:

a. PDGF-BB (becaplermin), [redacted]

b. Sodium carboxymethylcellulose, [redacted]

(b)(4)

c. sodium chloride, [redacted]

d. sodium acetate trihydrate, [redacted]

e. glacial acetic acid, [redacted]

f. methylparaben, [redacted]

g. propylparaben, [redacted]

h. m-Cresol, [redacted]

I. L-lysine hydrochloride, [redacted]

j. water for injection, [redacted]

Batch size will be [redacted]

III. Responsibilities:

OMJ Pharmaceuticals, San German, Puerto Rico:

a. acceptance of drug substance

b. testing of excipients

c. testing of container/closure systems

d. testing of in-process samples

e. *testing of finished drug substance

f. labeling

g. packaging

h. initial wharehousing

i. *stability testing of drug product

j. final arbitrater of final release and disposition of all components and final drug product

*except for mitogenesis assay

Ortho Biotech, Raritan, NJ:

a. Microbial limits testing for NaCMC

b. antimicrobial preservative effectiveness testing

c. microbial limits

McNeil Pharmaceutical, Raritan, NJ:

a. Distribution and Marketing

Franklin Distribution Center, Somerset, NJ:

a. Final Wharehousing of Drug Product

IV. Flow Diagram of Formulation:

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a. Drug Substance Preparation: [redacted] frozen drug substance are thawed and pooled into [redacted] container, store at 2-8°C. Typically, thawed drug substance can remain thawed at 2-8°C for 24-48 h and refrozen, if necessary. Thawed drug substance can be refrozen a maximum of three times and stored for a maximum of 18 days (total cumulative) at 2-8°C. Chiron stability studies (Vol., page 215) indicate stability at 5°C for 3 months (see below, Vol. 4, pages 38 and 215).

in-process test: OD at 280 nm

b. Buffer Preparation: [redacted] WFI, methylparaben, propylparaben add and mix [redacted]

(b)(4)

in-process test: [redacted]

c. Filter [redacted]

in-process test: Filter integrity

d. Gel Preparation: Add and mix [redacted]

(b)(4)

in-process test: agglomerates

e. Filter [redacted]

in-process test: Filter integrity

f. Add and Mix becaplermin

(b)(4)

g. Discharge gel to portable holding tank

in-process test: sample beginning, middle, and end of bulk gel for content uniformity, [redacted], viscosity and bioburden

h. Transfer bulk gel to In-Process Cold Storage (2 to 8°C)

i. Fill tubes, seal tubes

in-process test: sample beginning, middle and end for weight and tube integrity

j. Packaging of tubes and storage at 2-8°C

k. Final testing

V. Release Specifications for Drug Product

a. Appearance

Specification: clear, colorless to straw-colored

b. pH

Specification: [redacted]

c. Becaplermin (PDGF-BB) Content

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Specification: [redacted]

d. Biological Potency

Specification: [redacted] of label claim

e. SDS-PAGE, reduced and non-reduced

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Specification: conforms to standard; non-reduced with major band at [redacted] reduced with two major bands [redacted]

f. Preservatives: methylparaben, propylparaben, meta-cresol

(b)(4)

Specification: [redacted] of label

g. Microbial Limits

Specification: <10 CFU/g and the absence of S. aureus, E. coli, P. aeruginosa, β-hemolytic streptococci and C. albicins

Comment: While there is no release specification for the presence of bacteroides fragilis, it has been included in the preservative effectiveness test (see below, Vol. 4, page 134).

h. Antimicrobial Preservative Effectiveness

Specification:

Time	Bacteria	Yeast and Mold
48h	>/= 3	Not applicable (NA)
7 d	No Organism Recovered (NOR)	NA
14 d	NOR	>/= 2
21 d	NOR	No increase (NI)
28 d	NOR	NI

V. Container/Closure System

The drug product is packaged in prelabeled laminated tubes containing 2 g, 7.5 g or 15 g of regranex. The laminated tubes are provided by [~~~~] [~~~~~~~~~~~~~~~~]

(b)(4)

VI. Drug Product Stability

Initially in the BLA submission an expiration date of 15 months had been set for regranex when stored at 2-8°C. Stability data to justify this expiry had been provided for four lots of the proposed drug product manufactured at the commercial site and scale [~~~~~~] Stability studies are currently on-

going for three conformance lots. These studies have also addressed the stability of different size tubes of regranex (i.e. 2, 7.5 or 15 g).

[

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] **Thus, the expiration date for regranex gel stored at 2-8°C has been set at 9 months.**

Date of Manufacture (Vol. 4, pg. 206)

Date of manufacture is defined as the date when Becaplermin drug substance is incorporated into carboxymethylcellulose gel.

Volume 4

Chemistry, Manufacturing and Controls Information:

Page 6: Each lot of drug substance which comes from Chiron contains a certificate of analysis and is evaluated for identity using a dot blot immunoassay

Comment: the sponsor has been requested to perform a Western blot on either reduced or non-reduced drug substance, instead of a dot blot, to confirm the identity of the becaplermin and to confirm PDGF integrity. This suggestion was made by Kurt Stromberg during the OMJ inspection.

Page 38: Thawed drug substance can remain thawed at 2-8°C for 24-48 h and refrozen, if necessary. Thawed drug substance can be refrozen a maximum of three times and stored for a maximum of 18 days (total cumulative) at 2-8°C.

Page 134: Note that while there is no release specification for the presence of bacteroides fragilis, it has been included in the preservative effectiveness test.

Page 215: Chiron stability studies indicate stability of drug substance at 5°C for 3 months.

Pages 141-156: Certificates of analysis for the three conformance lots of drug product, TS-96-038, TS-96-071, and TS-96-072 were found to be acceptable.

Date of Manufacture (pg. 206)

Date of manufacture is defined as the date when Becaplermin drug substance is incorporated into carboxymethylcellulose gel.

Volume 5

The following SOPs were found to be acceptable:

A. Identity Immunoassay: Dot Blot (sponsor has been requested to replace this SOP for on with a Western to confirm identity)
B. Protein content
C. pH measurement
D. Viscosity
E. Tube testing machine for final drug product
F. Visual Appearance

G. PDGF content by HPLC

H. Bioassay: Human Foreskin Fibroblast Mitogenesis (DNA synthesis) Assay

I. SDS-PAGE

J. Preservative Content

K. Microbial Limits

L. Antimicrobial Preservative Effectiveness

Volume 8

The validation reports which support the Volume 5 SOPs were found in volume 8. These reports validated the SOPs and were found to be acceptable.